



Neurological Outcome Following Newborn Encephalopathy With and Without Perinatal Infection: A Systematic Review

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Background: Studies have suggested that neurological outcome may differ in newborns with encephalopathy with and without perinatal infection. We aimed to systematically review this association.

Methods: We conducted this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Studies were obtained from four databases including Pubmed, Embase, Web of Science, and The Cochrane Database. Newborns with encephalopathy with and without markers of perinatal infection were compared with regard to neurodevelopmental assessments, neurological disorders, and early biomarkers of brain damage. Risk of bias and quality of evidence were assessed by the Newcastle-Ottawa scale and Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Results: We screened 4,284 studies of which eight cohort studies and one case-control study met inclusion criteria. A narrative synthesis was composed due to heterogeneity between studies. Six studies were classified as having low risk of bias, while three studies were classified as having high risk of bias. Across all outcomes, the quality of evidence was very low. The neurological outcome was similar in newborns with encephalopathy with and without markers of perinatal infection.

Conclusions: Further studies of higher quality are needed to clarify whether perinatal infection may affect neurological outcome following newborn encephalopathy.

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Keywords: neonatal encephalopathy, hypoxic-ischemic encephalopathy, infection, therapeutic hypothermia, neurodevelopment

INTRODUCTION

Neonatal encephalopathy due to intrapartum-related events—newborn encephalopathy—is a major contributor to infant mortality and neurodevelopmental morbidity (1). When hypoxia-ischemia is the suspected cause of newborn encephalopathy, therapeutic hypothermia may be applied as neuroprotective treatment (2). However, some 50% of all newborns treated with hypothermia still develop unfavorable neurological outcomes (2, 3).

While hypoxia-ischemia may be commonly involved in newborn encephalopathy, the etiology remains multifactorial (4, 5). Perinatal infection is also associated with newborn encephalopathy (6–14). Ascending bacteria may spread to the fetus or result in fetal inflammatory response syndrome, characterized by systemic and local inflammation in the fetal organs including the brain (15, 16). Bacteria from the birth canal may also be transmitted during delivery leading to early-onset infection with similar activation of the newborn inflammatory system (17). Infection and inflammation in the central nervous system may cause encephalopathy and brain damage *per se* or act in combination with other insults such as hypoxia-ischemia (18–20). This *multiple-hit hypothesis* states that one insult could sensitize the fetal or newborn brain in order for secondary insults to have larger clinical impact (20–23). Several animal studies have found that endotoxin-induced inflammation prior to hypoxia-ischemia severely exacerbates brain injury in newborns (24–31). In addition to the possible aggravation of brain damage, both animal (32–37) and clinical studies (38–41) have suggested that infections may affect both the efficacy and safety of therapeutic hypothermia.

Accordingly, perinatal infection may interfere with the prognosis in newborns with encephalopathy. A systematic review of this association in humans may qualify the need for differential treatment in newborns with encephalopathy born by mothers with infection or with infection themselves. Therefore, the aim of this systematic review was to compare newborns with encephalopathy with and without markers of perinatal infection with regard to neurological outcome including neurodevelopmental assessments, neurological disorders, and early biomarkers of brain damage.

METHODS

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Supplementary A) (42). The protocol was registered 12th of May 2020 at the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020185717) (43). Two authors (MA and MVP) independently screened articles, assessed eligibility, extracted data, and analyzed risk of bias and quality of evidence. Any disagreements were resolved by discussion or by a third reviewer (TBH).

Terminology

Neonatal encephalopathy is a broad term including different etiologies, while hypoxic-ischemic encephalopathy may be used when hypoxia-ischemia is the most likely cause of the encephalopathy (44, 45). In this systematic review, we used the term “newborn encephalopathy” to emphasize our interest in insults surrounding the birth and the uncertainty with underlying causes. However, when discussing the individual studies, we continued the use of their specific terminology. In addition, no consensus definition of neonatal sepsis currently exists (46). Positive blood culture remains the golden standard of diagnosis. However, several neonates are believed to have sepsis without

ever having isolated the specific pathogen (47, 48). Again, we opted to continue the terminology and definition of sepsis used in each individual study.

Eligibility Criteria Studies

We only included peer-reviewed studies. Both observational studies and randomized controlled trials were eligible for inclusion, while case reports and case series were excluded. No restrictions by language or publication dates were applied.

Population

Newborns with a gestational age of ≥ 36 completed weeks or with a birth weight of ≥ 2500 g.

Exposure

Newborns with a diagnosis of neonatal encephalopathy or hypoxic-ischemic encephalopathy in combination with markers of bacterial infection in the mother or child during the perinatal period. Markers of maternal infection included clinical or histological chorioamnionitis, funisitis, and/or chorionic vasculitis. Markers of early-onset infection included infection proven by culture or molecular testing or suspected infection as assessed by the clinician based on clinical features, decision to initiate and continue antimicrobial treatment, and biomarkers including either white blood-cell counts, neutrophil counts, ratio of immature to total neutrophils, C-reactive protein, procalcitonin, or interleukins (IL-6, IL-8, or IL-10).

Comparators

Newborns with a diagnosis of neonatal encephalopathy or hypoxic-ischemic encephalopathy without the markers of bacterial infection in the mother or child during the perinatal period.

Outcome

The primary outcome was the composite outcome of (1) scales and tools for assessing neurodevelopmental function, (2) neurological disorders including seizure-, motor-, cognitive-, mental-, and behavioral disorders, and (3) mortality. The secondary outcomes were defined as the above outcomes assessed separately except for mortality. Furthermore, we included biomarkers of early brain damage such as magnetic resonance imaging (MRI) measures and MR spectroscopy, as well as conventional and amplitude-integrated electroencephalography (49, 50).

Information Sources and Search Strategy

The search strategy was developed by the authors and tested before use. The primary search was conducted 12 April 2021. Pubmed, Embase, Web of Science, and The Cochrane Database were searched by use of subject headings and free texts related to newborns, encephalopathy, and infection (Supplementary B). Our search was limited to human studies. References and citations from each included study were manually scrutinized for additional relevant studies.

Study Selection

The search results from each database were pooled using Endnote X9® and duplicates were removed. Rayyan QCRI was used in the screening process (51). Studies found by search were screened by title and abstract, while references and citations from included studies were screened by title only. All studies that seemingly met the eligibility criteria or provided insufficient information were extracted for full-text analysis. If any information regarding the eligibility criteria was missing, the study was excluded (Supplementary C).

Data Collection and Data Items

Data were extracted by a predefined data-collection form. To reduce errors and missing data plots, the data form was piloted prior to data extraction. Following items were extracted from each study: (1) title, authors, country, journal, year of publication, references, citations, funding sources, and conflicts of interest; (2) aim of the study, design, setting, and time-period; (3) number and characteristics of the newborns; (4) assessments of encephalopathy and whether the newborns received therapeutic hypothermia; (5) assessments of maternal and newborn infections; (6) assessments of neurological outcome; and (7) statistical methods and results (Supplementary D).

Risk of Bias in Individual Studies

The Newcastle-Ottawa Scale for cohort studies was used to evaluate the risk of bias. The studies were evaluated on the risk of bias in the domains: selection process, comparability between groups, and assessment of outcome. A total of four, two, and three points could be awarded in each domain, respectively. The risk of bias in the studies was rated as “low” when awarded 3–4 points in selection, 1–2 points in comparability, and 2–3 points in outcome; “fair” when awarded 2 points in selection, 1–2 points in comparability, and 2–3 points in outcome; and “high” when awarded 0–1 point in selection or 0 point in comparability or 0–1 point in outcome. When assessing comparability, one point was awarded if the study controlled for malformations. An additional point was awarded if the study controlled for gestational age, birth weight, gender, or metabolic diseases.

Synthesis of Results

No meta-analysis was performed due to the heterogeneity between the studies with regard to the assessment of encephalopathy, infection, and neurological outcome. A narrative synthesis of the results was made in accordance with Popay et al. (52). In studies with inadequate summary measures, a Chi-square test or Fischer’s exact test was performed to assess odds ratio with 95% confidence interval. Analyses were performed by GraphPad Prism version 8.0.0 for Mac (GraphPad Software, San Diego, California USA, www.graphpad.com).

Quality of Evidence

The quality of evidence was assessed in accordance with GRADE (53, 54). A total of five domains were evaluated including the risk of bias, directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias. Due to their observational

design, the studies started with an initial rating of low quality. The studies were then downgraded for serious limitations in any of the five domains and would only be upgraded if no downgrading had occurred. Accordingly, the quality of evidence could be rated as high, moderate, low, or very low.

Risk of Bias Across Studies

Publication bias was assessed qualitatively based on the characteristics of the included studies as an insufficient number of studies was included for formal test of asymmetry. Selective reporting bias was assessed by comparing the outcomes reported in the method section and the result section of the included studies.

RESULTS

Study Selection

A total of 4,256 studies were identified across all databases. After removal of duplicates, 3,254 studies were screened for inclusion. Of these, 55 studies were evaluated by full-text and seven studies were eligible for inclusion. Two additional studies were included following screening of 1,030 references and citations from already included studies. This led to inclusion of nine studies for this systematic review (55–63). An overview of the selection process is illustrated in the PRISMA flow diagram (Figure 1).

Study Characteristics

Designs and Populations

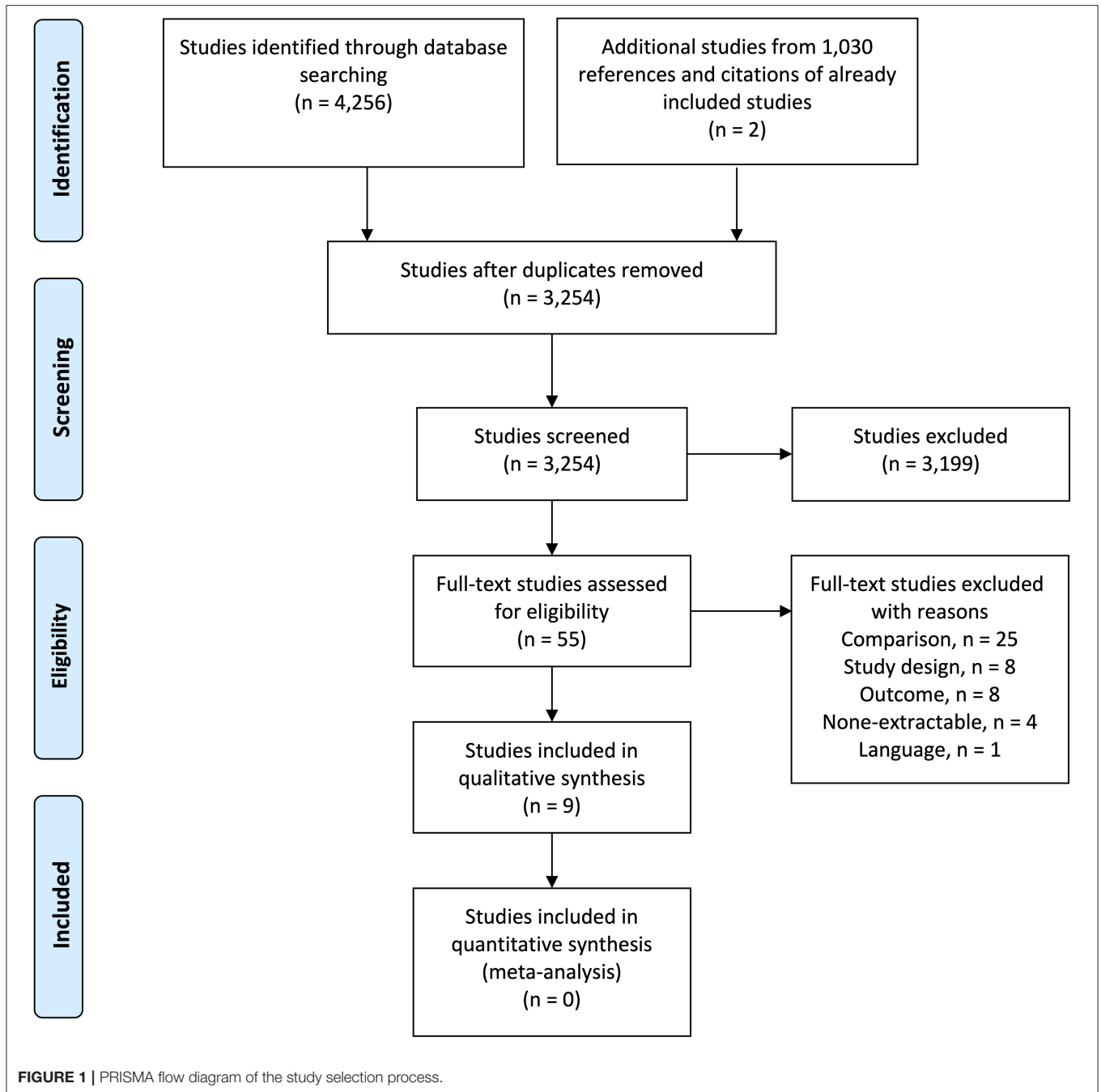
Eight cohort studies (55–61, 63) and one case-control study (62) were included. Table 1 provides number, gestational age, birth weight, and gender of the newborns, separated by infection status when possible. Three studies from the Netherlands have overlapping populations (56, 57, 61). Hakobyan et al. (56) only included historical controls (64). Newborns with encephalopathy fulfilled criteria for therapeutic hypothermia in seven studies (55–60, 63), while hypothermia was introduced midtrial in a single study (61). One study was conducted before the implementation of hypothermia (62).

Markers of Hypoxia-Ischemia

Table 2 provides the potential markers of hypoxia-ischemia, which was part of the inclusion criteria in each study. Six studies stated that they included newborns with encephalopathy and biochemical criteria suggestive of hypoxia-ischemia including low umbilical arterial pH and high base deficit (55, 58–61, 63). The occurrence of perinatal sentinel events as potential causes of hypoxia-ischemia was part of the criteria in five studies; however, the occurrence was not fully necessary for inclusion (55, 58–60, 63). Three studies solely stated that they included newborns with encephalopathy with signs of asphyxia or due to presumed hypoxia-ischemia (56, 57, 62). However, biochemical markers and other signs of fetal and neonatal distress were presented in the descriptive data of the studies.

Markers of Perinatal Infection

Seven studies investigated newborns born by mothers with markers of infection (57–63). Six studies stated that histological chorioamnionitis, funisitis, or chorionic vasculitis were assessed



by a blinded pathologist (57, 59–63), while one study stated that the diagnoses were obtained from placental pathology reports (58). Two studies investigated newborns with markers of infection (55, 56). Rao et al. (55) identified infections within seven days of life. Proven infection was defined by a positive culture (blood, urine, cerebrospinal fluid, airways), while suspected newborns had negative cultures but still received antimicrobial treatment for 7 to 10 days. Hakobyan et al. (56) included newborns who all showed clinical signs of sepsis within 48 h. In addition, the newborns had positive blood cultures,

positive surface cultures, or elevated C-reactive protein (≥ 50 mg/L). All newborns received antimicrobial treatment for at least 7 days.

Neurological Outcomes

Tables 3, 4 provide timing of neurological assessment in each study, which spanned from soon after birth to around 24 months of life. Neurodevelopmental outcomes were investigated in three studies (56, 57, 59). Hakobyan et al. and Frank et al. (56, 57) defined adverse neurological outcome as death,

TABLE 1 | Number, gestational age, birth weight, and male to female (M/F) ratio of the newborns in the studies investigating the association between newborn encephalopathy, perinatal infection, and neurological outcome.

Study and country	Groups	Number	Gestational age (weeks)	Birth weight (g)	M/F-ratio
Rao (55) ^a	Proven infection	36	40 (39–40)	3,471 (3,075–3,835)	22/14
USA	Probable infection	255	39 (38–40)	3,370 (2,990–3,771)	145/110
	No infection	1,243	39 (38–40)	3,260 (2,911–3,670)	693/550
Hakobyan (56) ^b Netherlands	Proven sepsis	14	40 (1.7)	3,658 (534)	7/7
	Probable sepsis	28	40 (1.5)	3,660 (726)	14/14
	No infection	308	40 (1.6)	3,401 (612)	164/144
Frank (57) ^a Netherlands	All neonates	76	40 (36–42)	3,455 (2,100–5,700)	41/35
Orrock (58) ^d USA	All neonates	28	>36	>1,800	NDA
Mir (59) ^b USA	All neonates	73	39 (2)	3,384 (607)	NDA
Lachapelle (60) ^b Canada	All neonates	103	39 (1.5)	3,411 (662)	58/45
Harteman (61) ^c Netherlands	All neonates	95	40 (36–42)	3,290 (2,030–5,500)	54/41
Hayes (62) ^d Ireland	All neonates	56	>36	NDA	NDA
Wintermark (63) ^b Canada	All neonates	23	39 (1.2)	3,385 (408)	13/10

NDA, no data available.

Gestational ages and birth weights presented as ^amedian (lower to upper quartile), ^bmean (standard deviation), ^cmedian (range), and ^dbased on inclusion criteria.

neurological disability (e.g., cerebral palsy), or abnormal Griffiths' neurodevelopmental quotient (<88 or 85) or Bayley Scales of Infant and Toddler Development-III (Bayley-III) score (<85). Mir et al. (59) also investigated a composite outcome consisting of death or low Bayley-III score (<85). MRI findings were investigated in seven studies (55, 57, 58, 60–63). Rao et al. (55) obtained MRI findings classified as either normal, abnormal, cortical injury, deep gray matter injury, or white matter injury. Frank et al. and Harteman et al. (57, 61) classified patterns of brain injury by MRI as normal, white matter/watershed injury, basal-ganglia-thalamus injury, or injury in both. Classification in similar manner based on Barkovich et al. (65) was used in three studies (58, 60, 62). Wintermark et al. (63) identified MRI findings showing evidence of hypoxic-ischemic brain injury. Two studies used postmortem brain examinations or cerebral ultrasound when MRI was unavailable (57, 60).

Risk of Bias Within Studies

Table 5 provides an overview of the points awarded by the Newcastle-Ottawa Scale. The studies failed to report on several of the selected risk factors for quality assessment and three studies failed to report on any of these (59, 60, 63). Rao et al. (55) excluded newborns with major congenital anomalies and found no difference between newborns with and without early-onset infection with regard to gestational age and gender, but observed that newborns with infections had higher birth weights. Hakobyan et al. (56) found no difference between newborns with and without early-onset sepsis with regard to gestational age, birth weight, and gender. Orrock et al. (58) excluded newborns

with major congenital abnormalities. Three studies excluded newborns with either chromosomal or metabolic disorders (57, 61, 62). In total, six studies were classified as having low risk of bias (55–58, 61, 62), while three studies were classified as having high risk of bias (59, 60, 63).

Results of Individual Studies

Maternal Infection

A summary of the results is presented in Table 3. The studies found no statistically significant difference in neurological outcome between newborns with encephalopathy born by mothers with and without markers of infection (57–63). Frank et al. and Mir et al. (57, 59) found tendencies toward more favorable neurodevelopment in newborns born by mothers with chorioamnionitis or funisitis. With regard to neuroimaging, most studies also reported tendencies toward more favorable MRI findings in newborns with maternal infections (57, 58, 60–62).

Early-Onset Infection

A summary of the results is presented in Table 4. Hakobyan et al. (56) found no difference in death or unfavorable neurodevelopment between newborns with neonatal encephalopathy with and without markers of early-onset sepsis. Rao et al. (55) similarly found no difference in MRI findings between newborns with hypoxic-ischemic encephalopathy with and without proven or suspected early-onset infections.

TABLE 2 | Possible markers of hypoxia-ischemia as part of inclusion criteria in the studies investigating the association between newborn encephalopathy, perinatal infection, and neurological outcome.

Study	Used terminology	Therapeutic hypothermia	Biochemical markers	Other evidence of neonatal distress ^a	Other evidence of fetal distress ^a	Multiorgan failure ^a
Rao (55)	Hypoxic-ischemic encephalopathy	Yes	Arterial cord pH ≤ 7 or BD ≥ 16 If unavailable or pH was between 7.01 and 7.15 or BD between 10 and 16, additional criteria were needed	Clinical encephalopathy Seizures Apgar score ≤ 5 Continuous need for ventilation Abnormal aEEG Neuroimaging of ischemia within 7 days of life	History of acute perinatal event Evidence of fetal distress (heart rate monitoring, umbilical cord Doppler, or biophysical profile)	Yes
Hakobyan (56) ^b	Neonatal encephalopathy with signs of asphyxia	Yes				
Frank (57) ^b	Neonatal encephalopathy with signs of asphyxia	Yes		Clinical encephalopathy Abnormal aEEG		
Orrock (58)	Hypoxic-ischemic encephalopathy	Yes	Arterial cord pH ≤ 7 or BD ≥ 16 If unavailable or pH was between 7.01 and 7.15 or BD between 10 and 15.9, additional criteria were needed	Clinical encephalopathy Seizures Apgar score ≤ 5 Continuous need for ventilation	History of acute perinatal event	
Mir (59)	Neonatal encephalopathy	Yes	Arterial cord pH ≤ 7 or BD ≥ 16 If unavailable or pH was between 7.01 and 7.15 or BD between 10 and 15.9, additional criteria were needed	Clinical encephalopathy Apgar score ≤ 5 Continuous need for ventilation	History of acute perinatal event	
Lachapelle (60)	Neonatal encephalopathy with signs of asphyxia	Yes	Arterial cord pH ≤ 7 or BD ≥ 16 Possibly blood gas <1 h of life with pH ≤ 7 or BD ≥ 16	Clinical encephalopathy Apgar score ≤ 5 Continuous need for ventilation Abnormal aEEG	History of acute perinatal event	
Harteman (61)	Neonatal encephalopathy after presumed hypoxia-ischemia	Midtrial	Arterial cord pH <7.1	Clinical encephalopathy Seizures Delayed onset of respiration Apgar score ≤ 7 Thompson score >7	Late decelerations on fetal monitoring	Yes
Hayes (62) ^b	Neonatal encephalopathy after presumed hypoxia-ischemia	No				
Wintermark (63)	Hypoxic-ischemic encephalopathy	Yes	Possibly arterial cord pH ≤ 7 or BD ≥ 16 Possibly blood gas <1 h of life with pH ≤ 7 or BD ≥ 16	Clinical encephalopathy Apgar score ≤ 5 Continuous need for ventilation Abnormal aEEG	History of acute perinatal event Biophysical profile	Yes

BD, base deficit; aEEG, amplitude-integrated electroencephalogram.

^aNot all criteria fully necessary for inclusion, ^bPresence of biochemical markers and evidence of fetal and neonatal distress was presented in the descriptive data of the studies.

TABLE 3 | Odds ratios (OR) with 95% confidence intervals (CI) of unfavorable neurological outcome between newborns with encephalopathy with and without maternal infection.

Study	Exposure	Adverse outcome	Follow-up	Exposed	Comparators	OR (95% CI)
Frank (57)	Chorioamnionitis Funisitis	Death, cerebral palsy, or Griffiths' neurodevelopment quotient <85 or Bayley-III <85	18–24	11/29 (38 %)	24/47 (51 %)	0.6 (0.2–1.4)
			months of age	4/12 (33 %)	31/64 (48 %)	0.5 (0.2–1.8)
Mir (59)	Chorioamnionitis Chorioamnionitis with fetal response	Death or Bayley-III score <85	18–24	26/47 (55 %)	14/26 (54 %)	1.1 (0.7–2.8)
			months of age	14/32 (44 %)	26/41 (63 %)	0.4 (0.2–1.1)
Frank (57)	Chorioamnionitis Funisitis	MRI evidence of WM/WS, BGT, or near total injury	NDA	15/29 (52 %)	33/46 (72 %)	0.4 (0.2–1.1)
Orrock (58)	Chorioamnionitis	Died or MRI evidence of WM/WS or BGT damage	10–12 days of age	5/12 (42 %)	43/63 (68 %)	0.3 (0.1–1.2)
				3/9 (33 %)	9/19 (47 %)	0.6 (0.1–2.9)
Lachapelle (60)	Chorioamnionitis with or without vasculitis	MRI evidence of WM/WS or BGT damage		12/30 (40 %)	41/73 (56 %)	0.5 (0.2–1.2)
Harteman (61)	Chorioamnionitis Funisitis	MRI evidence of injury in WM/WS, BGT, or WM/WS with BGT involvement	2–15 days of age	24/44 (55 %)	37/51 (73 %)	0.5 (0.2–1.0)
				13/23 (56 %)	48/72 (67 %)	0.7 (0.2–1.6)
Hayes (62)	Funisitis Vasculitis	MRI evidence of injury in WS, BG, both, or other brain injuries	Before 1 month of age	1/3 (33 %)	34/59 (58 %)	0.4 (0.1–3.3)
				12/19 (63 %)	22/37 (59 %)	1.2 (0.4–3.5)
Wintermark (63)	Chorioamnionitis Chorioamnionitis with vasculitis	MRI evidence of hypoxic-ischemic brain injury	NDA	4/8 (50 %)	3/15 (20 %)	4.0 (0.7–20.4)
				3/5 (60 %)	4/18 (22 %)	6.0 (0.8–41.4)

NDA, no data available; MRI, magnetic resonance imaging; WM/WS, white matter/watershed; BGT, basal-ganglia-thalamus; Bayley-III, Bayley Scales of Infant and Toddler Development-III.

Odds ratios with 95% confidence intervals were calculated by Fisher's exact test. Adverse outcomes in bold indicate our primary outcomes.

TABLE 4 | Odds ratios (OR) with 95% confidence intervals (CI) of unfavorable neurological outcome in newborns with encephalopathy with and without early-onset infection.

Study	Exposure	Adverse outcome	Follow-up	Exposed	Comparators	OR (95% CI)
Hakobyan (56)	Proven or probable sepsis	Death, cerebral palsy, neurodevelopmental impairment of >3 months, Griffith's neurodevelopment quotient <88, or Bayley-III <85	At least 18 months	14/42 (33 %)	140/308 (45 %)	0.6 (0.3–1.2)
Rao (55)	Suspected infection	Abnormal MRI findings	NDA	31/255 (12 %)	155/1,243 (12 %)	1.0 (0.6–1.4)
		Cortical injury on MRI		29/255 (11 %)	140/1,243 (11 %)	1.0 (0.7–1.5)
		Deep gray matter injury on MRI		49/255 (19 %)	197/1,243 (16 %)	1.3 (0.9–1.8)
		White matter injury on MRI		46/255 (18 %)	166/1,243 (13 %)	1.4 (1.0–2.0)
		Normal MRI findings		78/255 (30 %)	404/1,243 (33 %)	0.9 (0.7–1.2)
	Confirmed infection	Abnormal MRI findings		8/36 (22 %)	155/1,243 (12 %)	2.0 (0.9–4.4)
		Cortical injury on MRI		4/36 (11 %)	140/1,243 (11 %)	1.1 (0.4–3.0)
		Deep gray matter injury on MRI		8/36 (22 %)	197/1,243 (16 %)	1.5 (0.7–3.2)
		White matter injury on MRI		5/36 (14 %)	166/1,243 (13 %)	1.0 (0.4–2.6)
		Normal MRI findings		10/36 (28 %)	404/1,243 (33 %)	0.8 (0.4–1.7)

NDA, no data available; MRI, magnetic resonance imaging; Bayley III, Bayley Scales of Infant and Toddler Development-III.

Odds ratios with 95% confidence intervals were calculated by Chi-square test or Fisher's exact test. Adverse outcomes in bold indicate our primary outcomes.

Therapeutic Hypothermia

The studies found no statistically significant difference between hypothermia-treated newborns with encephalopathy with and without markers of perinatal infection (55–60, 63).

Quality of Evidence

We found that the quality of evidence across all outcomes was very low according to the GRADE assessment. This was mainly due to a concern related to risk of bias within the studies and the small number of included newborns. Furthermore, early MRI

findings as proxy measures for neurodevelopment subjected the studies to downgrading for indirectness (53, 54).

Risk of Bias Across Studies

Selective reporting bias was not identified. Several of the studies reported no difference in neurological outcome between newborns with and without markers of perinatal infections. Furthermore, the association between perinatal infections and neurological outcome was not the primary aim in several studies (55, 57–63). Therefore, publication bias seems improbable.

TABLE 5 | Points awarded by the Newcastle-Ottawa Scale to the included studies investigating the association between newborn encephalopathy, perinatal infection, and neurological outcome.

Study	Representativeness of exposed cohort ^a	Selection of non-exposed ^b	Ascertainment of exposure ^c	Presences of outcome of interest ^d	Comparability ^e	Assessment of outcome ^f	Enough follow-up ^g	Adequacy of follow up ^h	Risk of bias
Rao (55)	A (*)	A (*)	A (*)	B (*)	A, B (**)	B (*)	A (*)	D	Low
Hakobyan (56)	A (*)	B	A (*)	A (*)	B (*)	B (*)	A (*)	B (*)	Low
Frank (57)	B (*)	A (*)	A (*)	A (*)	A, B (**)	B/D (*) ⁱ	A (*)	A (*)	Low
Orrock (58)	C	A (*)	A (*)	A (*)	A (*)	A (*)	A (*)	A (*)	Low
Mir (59)	A (*)	A (*)	A (*)	A (*)		A (*)	A (*)	A (*)	High
Lachapelle (60)	B (*)	A (*)	A (*)	A (*)		A (*)	A (*)	A (*)	High
Harteman (61)	B (*)	A (*)	A (*)	A (*)	A, B (**)	D	A (*)	A (*)	Low
Hayes (62)	B (*)	A (*)	A (*)	A (*)	A, B (**)	A (*)	A (*)	C	Low
Wintermark (63)	A (*)	A (*)	A (*)	A (*)		B (*)	A (*)	A (*)	High

Studies were rated as “low risk” when given 3–4 points (*) in selection and 1–2 points (*) in comparability and 2–3 points (*) in outcome; “fair risk” when given 2 points (*) in selection and 1–2 points (*) in comparability and 2–3 points (*) in outcome; and “high risk” when given 0–1 point (*) in selection or 0 point (*) in comparability or 0–1 point (*) in outcome.

^aRepresentativeness of the exposed cohort, a) truly representative, b) somewhat representative, c) selected group, and d) no description; ^bSelection of the non-exposed cohort, a) drawn from the same community, b) drawn from a different source, and c) no description; ^cAscertainment of exposure, a) secure record, b) structured interview, c) written self-report, and d) no description; ^dDemonstration that outcome of interest was not present at start of study, a) yes and b) no; ^eComparability of cohorts or cases and controls, a) study controls for malformation and b) study controls for either metabolic diseases, gestational age, birth weight, or gender; ^fAssessment of outcome, a) independent blind assessment, b) record linkage, c) self-report, and d) no description; ^gFollow-up long enough for outcomes to occur, a) yes and b) no; ^hAdequacy of follow up of cohorts, a) complete follow up, b) subjects lost to follow up unlikely to introduce bias, >5% follow up or description provided of those lost, c) follow up rate <5% and no description of those lost, and d) no statement; ⁱB for assessment of long-term neurodevelopmental outcome and D for assessment of magnetic resonance imaging.

DISCUSSION

Summary of Evidence

Based on the included studies, the presence of perinatal infection does not seem to impact neurological outcome in newborns with encephalopathy. However, the quality of evidence was very low.

Markers of maternal infection have been associated with newborn encephalopathy (6–12). However, we found no further association with worse neurological outcome. Some studies on maternal infection were excluded from this systematic review, despite having some relevance (**Supplementary C**). Nelson et al. (66) found that the combination of perinatal sentinel events and markers of maternal infection was associated with an increased risk of cerebral palsy compared with perinatal sentinel events alone. Jenster et al. (67) investigated newborns with clinical and biochemical evidence of hypoxia-ischemia including 5-min Apgar score ≤ 5 and arterial cord pH < 7.1 and base deficit > 10 . By contrast, they found that chorioamnionitis was associated with more favorable MRI findings at around 5 days of age and more favorable neurodevelopment assessed by Bayley-II or III at around 30 months of age. Early-onset infections may be more prevalent in newborns with encephalopathy and are associated with increased mortality (13, 14). However, as with maternal infections, we found no difference in neurological outcome between newborns with

encephalopathy with and without early-onset infection. Both included studies on early-onset infections had a limited number of newborns with positive cultures. Hakobyan et al. (56) analyzed the combined number of newborns with documented and suspected sepsis. Only a smaller fraction ($< 1/3$) considered to have an infection had positive culture, making the diagnosis less well defined. Furthermore, the study only included historical controls, which further limits the quality of evidence. Again, some studies on early-onset infection with some relevance for the topic were excluded (**Supplementary C**). Scheidegger et al. (68) found no difference in the Sarnat Staging during the first days of life between newborns with hypoxic-ischemic encephalopathy with and without early-onset sepsis (69). However, Jenster et al. (67) found early-onset sepsis to be associated with worse neuromotor function at around 30 months of age in newborns with clinical and biochemical markers of hypoxia-ischemia. In addition, when combining newborns with encephalopathy treated with and without hypothermia from a recent randomized controlled trial in low- and middle-income countries, culture-positive early- and late-onset sepsis were associated with increased risk of death or disability at 18 months (39).

Animal studies have suggested that infectious and inflammatory exposure before hypoxia-ischemia exacerbate newborn brain injury (24–31). Several biological mechanisms

have been suggested to explain these findings (70–86). However, this systematic review of human studies was not able to substantiate these findings. This may be due to more heterogeneity inherent in clinical compared to experimental studies. A previous study found perinatal sentinel events, as potential causes of hypoxia-ischemia, only to be present in some 15% of newborns with encephalopathy (8). The timing between different perinatal insults may also have influenced the neurological outcome. Animal studies have found that lipopolysaccharides from *Escherichia coli* administered 4 h, 6 h, and 72 h before hypoxia-ischemia result in more severe brain damage, while lipopolysaccharides administered 24 h before hypoxia-ischemia had neuroprotective effects (24, 25, 86, 87). Therefore, both positive and negative conditioning may occur in the fetal or newborn brain when exposed to multiple insults (88). This may explain the findings of the included study by Harteman et al. (61), who found that newborns with hypoxic-ischemic encephalopathy born by mothers with chorioamnionitis had the highest incidence of both normal and most severe MRI findings.

Several newborns with encephalopathy due to presumed hypoxia-ischemia still develop unfavorable neurological outcomes despite treatment with therapeutic hypothermia (2, 3). Several reviews have postulated that therapeutic hypothermia may be contraindicated in newborns with encephalopathy and infection (19, 20, 89, 90). This systematic review found similar neurological outcome between hypothermia-treated newborns with encephalopathy with and without markers of perinatal infection (55–60, 63). However, due to the very low quality of evidence across all outcomes, this concern may still be valid. To our knowledge, no randomized clinical trial has sufficiently investigated the neuroprotective effect of hypothermia in newborns with encephalopathy and perinatal infection, although no association between hypothermia and the risk of sepsis has been found (2). Therapeutic hypothermia has been shown to delay C-reactive protein response and to suppress white blood-cell count (91, 92). These findings may partly explain the reduced efficacy of hypothermia observed in low- and middle-income countries (where infections may be more prevalent) (38, 39), and the increased risk of mortality and prolonged shock observed in hypothermia-treated adults with meningitis and sepsis (40, 41). Furthermore, animal studies have found hypothermia to have limited neuroprotective effect following lipopolysaccharide-sensitized hypoxia-ischemia (32–37, 93). Both studies on early-onset infections included in this systematic review reported an overrepresentation of Gram-positive bacteria (55, 56). Contrarily, animal studies have found hypothermia to have some neuroprotective effect following sensitization by endotoxins deriving from Gram-positive bacteria (34, 94).

Strengths and Limitations

We conducted this systematic review according to the PRISMA guidelines (42). We followed a preregistered protocol. We conducted a systematic search across four different databases. To minimize bias, each step was performed independently by

two reviewers including screening of studies, data collection, and risk of bias and quality of evidence assessment. However, several limitations have to be considered. Newborn encephalopathy may arise from different etiologies including hypoxia-ischemia, infection and inflammation, placental pathologies, and more (5). These factors may alone or together affect the fetal or newborn brain. In the included studies, newborn encephalopathy may have occurred due to various factors and interactions. However, most studies presented criteria suggestive of both hypoxia-ischemia and perinatal infection, indicating that these factors were involved to some degree. The assessments of neurological outcomes may also be problematic. Most studies reported MRI findings, which not necessarily correlates with the neurodevelopmental outcome (95, 96). Furthermore, the longest follow-up time in the included studies was around 24 months of age. It would have been interesting to observe whether any differences in neurological outcome would develop throughout childhood and adolescence (97). Furthermore, due to inadequate reporting in several studies, we were unable to reject that the reference groups also contained mothers or newborns exposed to perinatal infections. This have likely biased the studies toward findings of no difference. At last, most included studies also contained small number of newborns and the comparability between newborns with and without perinatal infections was limited. This led to imprecision of the effect sizes and a high possibility of risk of bias. A meta-analysis could have increased the precision; however, the included studies were deemed to heterogeneous.

CONCLUSION

We found no difference in neurological outcome between newborns with encephalopathy with and without markers of perinatal infection. However, the current quality of evidence within this subject is very low. Therefore, further studies are needed with larger sample sizes, longer follow-up time, less risk of bias, and more detailed description of populations with reports of possible etiologies and interactions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

MA, MP, TA, KK, and TH designed the study. MA and MP undertook data collection and analysis. MA drafted the manuscript. All authors have critically reviewed the drafted manuscript and have approved the manuscript and agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fped.2021.787804/full#supplementary-material>

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